Pergamon

Tetrahedron 54 (1998) 2931–2940

TETRAHEDRON

Catalytic Hydrogenation Causes C-Benzyl Bond Cleavage in 6-Amino-7,7-dibenzyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine: an Example Indicating Novel Route to 6-Amino-7-benzyl-5*H*-pyrrolo--[3,2-*d*]pyrimidines and Related Compounds

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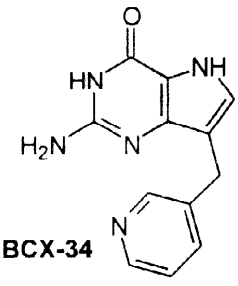
Received 2 December 1997; revised 12 January 1998; accepted 15 January 1998

Abstract: 7-Benzyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (**8**) and 6-amino-7,7-dibenzyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (**10**) were prepared by reductive cyclization of the corresponding 6-(1-cyanoalkyl)-5-nitropyrimidines. Catalytic hydrogenation of compound **10** causes a C-C bond cleavage between carbon C-7 and one of the geminal benzyl groups. It leads to the formation of 6-amino-7-benzyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (**12**) which was spontaneously oxidized by air to 6-amino-7-benzyl-2,4-dimethoxy-7-hydroxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (**13**).

INTRODUCTION

9-Deazapurine derivatives,[1-8] especially 9-arylmethyl-9-deazaguanines, are known as potent inhibitors of purine nucleoside phosphorylase (PNP, EC 2.4.2.1). PNP is considered an essential enzyme in the purine salvage pathway, catalysing the reversible phosphorolysis of guanosine, inosine and their 2-deoxyribonucleoside congeners to the free base and ribose-α-1-phosphate or 2-deoxyribose-α-1-phosphate. Genetic deficiency of PNP is generally associated with severe selective impairment in T-, but not B-lymphocyte function. If PNP is blocked, then T-cells should be unable to divide and proliferate. This profile suggests that PNP inhibitors might be useful in the treatment of T-cell proliferative diseases, such as T-cell leukemia or T-cell lymphoma, in the suppression of the tissue rejection after organ transplantation, and in the treatment of T-cell-mediated autoimmune diseases such as rheumatoid arthritis and psoriasis. From the most potent inhibitors of PNP, Peldesine (BCX-34, Fig. 1) is now undergoing clinical trials.[9,10]



BCX-34

Figure 1.

RESULTS AND DISCUSSION

In our previous publications we described the synthesis of 7-alkyl-5*H*-pyrrolo[3,2-*d*]pyrimidines **1** and 6-amino-7,7-dialkyl-7*H*-pyrrolo[3,2-*d*]pyrimidines **2** (Fig. 2) which exhibit two possible arrangements of the π-electronic system in the 9-deazapurine skeleton.[11,12] As a continuation of this study, we now report preparation of these two types of pyrrolo[2,3-*d*]pyrimidines with the benzyl group(s) at position 7 (ref.[13]).

Alkylation of the nitrile **3** (ref.[14,15]) with benzyl bromide afforded the mono- **4** and disubstituted product **5** (Scheme 1). Reduction of compound **4** with sodium dithionite in the methanol - water 1 : 1 mixture provided the

0040-4020/98/$19.00
PII: S0040-4020(98)00045-3

corresponding amine **6**. The amine **6** was converted to the acetate **7** by treatment with acetic anhydride in pyridine. Hydrogenation of the nitro derivative **4** or amine **6** gave the 5*H*-pyrrolo[3,2-*d*]pyrimidine **8**. On the other hand, the dithionite reduction of the disubstituted nitro derivative **5** required higher temperature probably because of a sterical hindrance caused by the two benzylic groups. The products were the amine **9** and the 6-amino-7*H*-pyrrolo[3,2-*d*]-pyrimidine **10** (ratio approx. 3 : 2). The cyclization of the amine **9** to compound **10** can be easily achieved by treatment with acetic acid. For further structural elucidation, compound **10** was converted to the acetate **11**. In contrast to the previously described 7,7-dialkyl-7*H*-pyrrolo[3,2-*d*]pyrimidines **2** which are stable on hydrogenation, the hydrogenation of the 7,7-dibenzyl derivative **10** (or its precursors **5** and **9**) effected a C-C bond cleavage resulting in removal of one of the geminal benzyl groups in position 7. Our explanation of this C-C bond scission is based on its similarity with a labile C-C bond in 1,2-diarylethanes and related compounds.[16] The benzylic character of C-7 carbon is shown in ^{13}C NMR spectrum (see below). The main product of the hydrogenation was unstable compound **12** whose spontaneous oxidation by air (and a subsequent cleavage of the supposed peroxide intermediate) provided the hydroxy derivative **13**. The same product was obtained by treatment of the crude derivative **12** with hydrogen peroxide. The unstable compound **12** was fully characterized as the acetate **14**. Acetylation of the hydroxy derivative **13** by heating with acetic anhydride in acetic acid gave the diacetate **15**. When acetic anhydride in pyridine was used, the diacetate **15** was accompanied with a small amount of the lactam **16**.

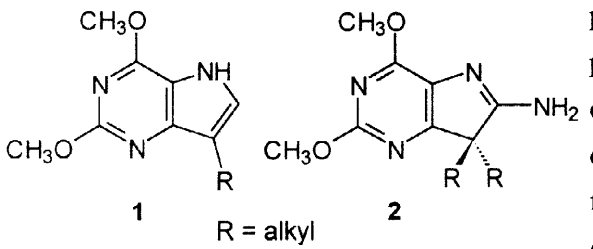
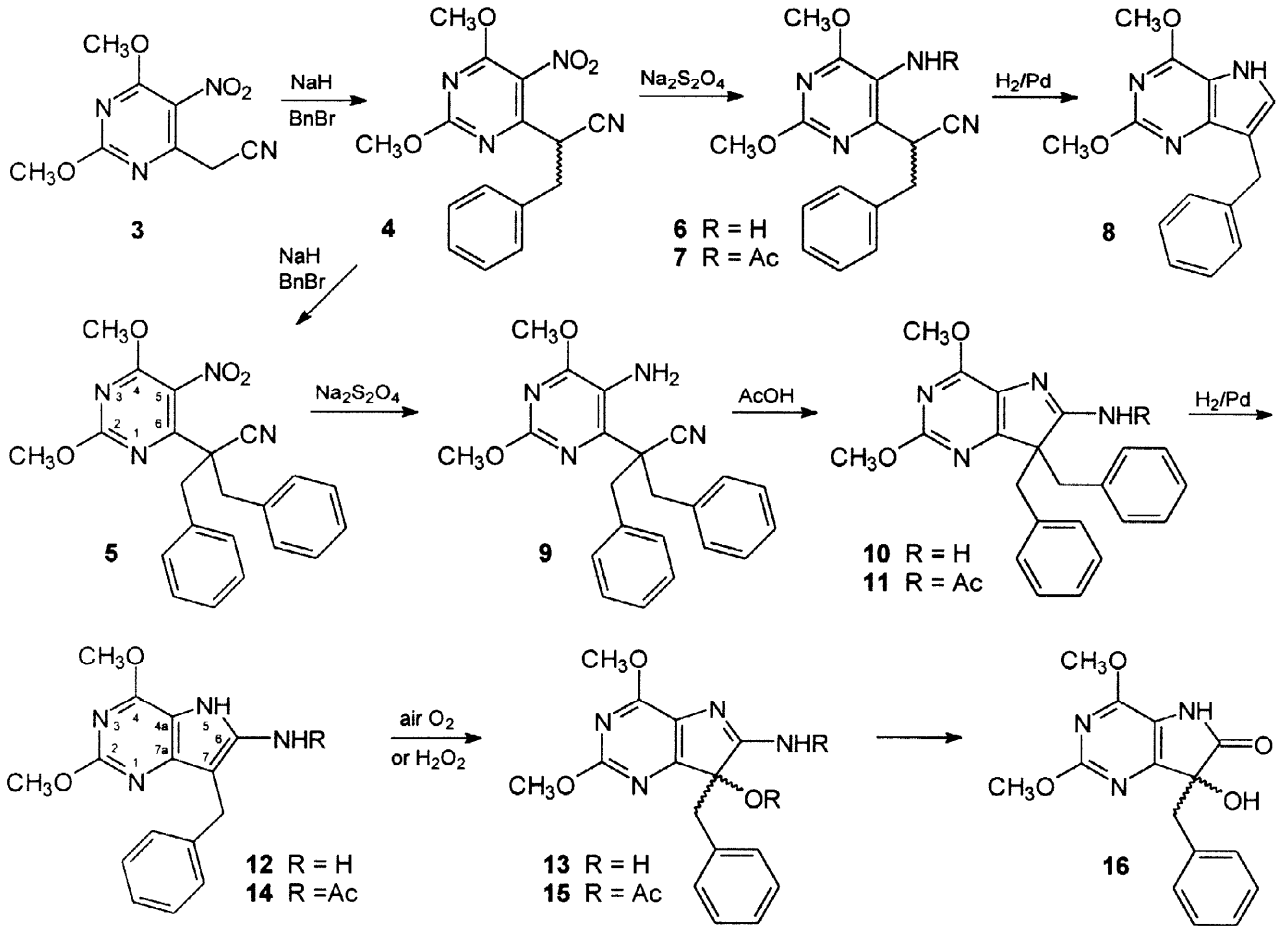


Figure 2.

The structural assignment of compounds **4** - **16** is based on ^{1}H and APT as well as proton-coupled ^{13}C NMR spectra (Tab. 1 - 4, Fig. 3). In the pyrimidine derivatives **4** - **7**, and **9**, assignment of the quaternary carbons is based on their couplings with the surrounding protons. The carbons C-2 and C-4 give quartets due to a characteristic coupling with protons of the methoxy groups [$^{3}J(C,H) = 3.9$ Hz]. The absence of other interactions and small difference between their chemical shifts does not allow unequivocal experimental distinguishing between C-2 and C-4. Our tentative assignment is mainly based on the characteristic upfield shifts (~3 and ~8 ppm) for C-2 and C-4 when the nitro group is reduced to the amino function.[11] Signals of the carbon atoms C-5 and C-6 were assigned from the couplings with the surrounding protons of the substituents in position 5 and 6. The presence of the N-acetyl group in compound **7** is clearly manifested in ^{1}H and ^{13}C NMR spectra. The cyano group was evidenced by the characteristic band (ν_{CN} ~ 2250 cm^{-1}) in IR as well as by the signal at ~119 ppm in ^{13}C NMR spectra.

^{1}H NMR spectra of 5*H*-pyrrolo[3,2-*d*]pyrimidines **8**, **12**, and **14** are characterized by symmetry equivalence of the benzylic CH_2 protons (singlet at ~3.9 ppm) and the lowfield signal (~11 ppm) of the pyrrole NH proton. In their ^{13}C NMR spectra, two additional sp^2-carbon signals appeared in comparison with the above pyrimidines. The carbon signals assignment was established on the basis of their couplings with the surrounding protons. In compound **12**, the presence of the 6-NH_2 group is indicated by two-proton signal at 5.64 ppm. The acetylation at this 6-amino group in the derivative **14** is evidenced by the characteristic signals of N-acetyl group in ^{1}H and ^{13}C NMR spectra and the significant substitution effects at carbons in positions 6, 7, 4a, and 7a.



Scheme 1.

In 7*H*-pyrrolo[3,2-*d*]pyrimidines **10**, **11**, **13**, and **15**, the location of the double bond between N-5 and C-6 is manifested by the lowfield signal of the sp^2-carbon C-6 (163 - 174 ppm) and, on the other hand, by the chemical shift of carbon C-7 (60 - 85 ppm) which indicates its sp^3-character. Two-proton signal of NH_2 at 7.2 and 7.3 ppm in compounds **10** and **13** excludes the tautomeric *imino*-form with an exocyclic C=N bond. The loss of symmetry plane in compounds **13** and **15**, and hindered rotation in dibenzyl derivatives **10** and **11** lead to the non-equivalence of benzylic CH_2 protons. In compound **13**, the location of the tertiary hydroxy group [δ(OH) = 6.25 s] at C-7 is clearly evidenced by the couplings with the surrounding carbons [J(OH, C-7) ~ 2.4; J(OH, C-7a) ~ 3.7 and J(OH, C-Ph) = 3.5 Hz]. In diacetate **15**, two characteristic signals of the acetyl groups as well as the corresponding substituent effects, caused by them on the chemical shifts of carbon atoms in pyrrole ring, were observed. In comparison to compounds **13** and **15**, the geminal dibenzyl derivatives **10** and **11** exhibit (besides double intensities of benzyl signals) the expected upfield shift of C-7 signals (60 and 63 ppm).

The main difference between the side product **16** and the parent hydroxy derivative **13** consists in the absence of the 6-amino group and in the presence of one-proton signal at 10.24 ppm which is analogous to the pyrrole NH in derivative **8**. The carbonyl group is evidenced by the characteristic bands in IR ($\nu_{C=O}$: 1743, 1714, 1665 cm^{-1}). The further structural assignment is mainly based on the proton-coupled ^{13}C NMR spectrum (Fig. 3).

Table 1. ^{1}H NMR Spectra: Chemical Shifts and Coupling Constants.

Proton	4	5	6	7	8	9
NH_2			4.76 s			4.41 s
NH				9.40 s	11.50 bs	
H-6					7.32 d (1.5)	
CH-CN	4.83 dd (5.8; 9.3)		4.76 dd (6.3; 9.1)	4.41 dd (5.6; 9.5)		
CH_a-Ph	3.32 dd (13.4; 5.8)	3.72 d (2H) (13.4)	3.21 dd (13.7; 6.3)	3.17 dd (13.7; 5.6)	3.95 s (2H)	3.75 d (2H) (13.7)
CH_b-Ph	3.21 dd (13.4; 9.3)	3.34 d (2H) (13.4)	3.15 dd (13.7; 9.1)	3.12 dd (13.7; 9.5)		3.24 d (2H) (13.7)
OCH_3	4.06 s 4.03 s	4.04 s 3.98 s	3.92 s 3.82 s	3.92 s 3.91 s	4.00 s 3.88 s	3.91 s 3.65 s
Ac				2.08 s		
Ph	7.34 m (4H) 7.29 m (1H)	7.32 m (8H) 7.27 m (2H)	7.32 m (4H) 7.25 m (1H)	7.33 m (2H) 7.26 m (3H)	7.32 m (2H) 7.24 m (2H) 7.13 m (1H)	7.22 m (6H) 7.15 m (4H)

Table 2. ^{13}C NMR Spectra: Chemical Shifts.

Carbon	4	5	6	7[b]	8[c]	9
C-2	163.48[a]	162.31[a]	160.84	162.51	156.91	161.83
C-4	164.02[a]	163.75[a]	155.81	167.35	159.28	154.92
C-5	128.44	130.41	122.41	111.57		122.59
C-6	159.92	155.88	141.63	160.84	128.67	141.84
CN	118.19	117.95	119.66	118.95		121.20
C-CN	37.18	50.56	34.38	36.44		51.61
C-Ph	37.94	43.86 (2C)	36.48	37.52	29.76	41.41 (2C)
OCH_3	56.26 56.23	56.30 56.17	54.31 54.13	55.07 54.77	54.01 53.37	54.51 53.99
Ph	136.29 129.27 (2C) 128.78 (2C) 127.56	134.60 (2C) 130.23 (4C) 128.52 (4C) 127.77 (2C)	137.26 129.33 (2C) 128.51 (2C) 127.12	136.90 129.21 (2C) 128.71 (2C) 127.31	141.91 128.67 (2C) 128.36 (2C) 125.82	135.83 (2C) 130.18 (4C) 128.16 (4C) 127.24 (2C)

a - The assignment of signals may be interchanged.
b - δ(N-Ac): 169.74; 22.77.
c - δ(C-4a) = 111.33; δ(C-7) = 114.12; δ(C-7a) = 149.71.

Table 3. ^{1}H NMR Spectra: Chemical Shifts and Coupling Constants.

Proton	10	11	12	13	14	15	16
NH_2	7.31 s		5.64 s	7.22 s			
NH		10.94 s	10.37 s		11.26 s 10.40 s	10.92 s	10.24 s
CH_a-Ph	3.27 d (2H) (13.2)	3.69 d (2H) (13.2)	3.79 s (2H)	3.22 d (12.4)	3.94 s (2H)	3.54 d (12.7)	3.17 d (12.2)
CH_b-Ph	3.24 d (2H) (13.2)	3.28 d (2H) (13.2)		3.16 d (12.4)		3.32 d (12.7)	3.08 d (12.2)
OH				6.25 s			6.46 s
OCH_3	3.93 s 3.67 s	4.02 s 3.76 s	3.91 s 3.81 s	3.88 s 3.78 s	3.98 s 3.84 s	3.91 s 3.86 s	3.91 s 3.85 s
Ac		2.20 s			2.11 s	2.22 s 2.10 s	
Ph	7.05 m (6H) 6.88 m (4H)	7.05 m (6H) 6.76 m (4H)	7.32 m (2H) 7.19 m (2H) 7.08 m (1H)	7.05 m (3H) 6.87 m (2H)	7.26 m (2H) 7.21 m (2H) 7.11 m (1H)	7.12 m (3H) 6.72 m (2H)	7.10 m (3H) 6.85 m (2H)

Table 4. ^{13}C NMR Spectra: Chemical Shifts.

Carbon	10	11	12	13	14	15	16
C-2	157.26[a]	159.29[a]	152.62[a]	158.29[a]	159.46[a]	159.70[a]	154.84[a]
C-4	159.60[a]	161.97[a]	159.33[a]	160.48[a]	155.85[a]	162.31[a]	160.99[a]
C-4a	130.38	127.32	104.64	129.22	106.96	125.83	117.28
C-6	172.88	169.74	148.83	173.86	150.03	163.28	176.61
C-7	60.34	63.21	91.74	81.96	101.66	85.43	76.90
C-7a	167.90	167.00	153.66	166.76	136.33	164.60	159.79
C-Ph	41.42 (2C)	39.62 (2C)	27.33	42.28	27.51	39.37	42.16
OCH_3	54.55 53.00	55.04 53.52	53.65 52.75	54.98 53.71	53.99 53.37	55.04 53.78	54.86 53.90
Ac		170.57 25.15			169.92 23.27	169.86 24.66 168.53 20.35	
Ph	136.22 (2C) 129.51 (4C) 127.77 (4C) 126.52 (2C)	135.74 (2C) 128.96 (4C) 128.05 (4C) 126.84 (2C)	142.71 128.51 (2C) 128.06 (2C) 125.46	134.79 130.13 (2C) 128.19 (2C) 127.08	141.46 128.48 (2C) 128.25 (2C) 125.72	131.75 129.77 (2C) 127.92 (2C) 127.38	134.12 129.92 (2C) 128.02 (2C) 126.87

a - The assignment of signals may be interchanged.

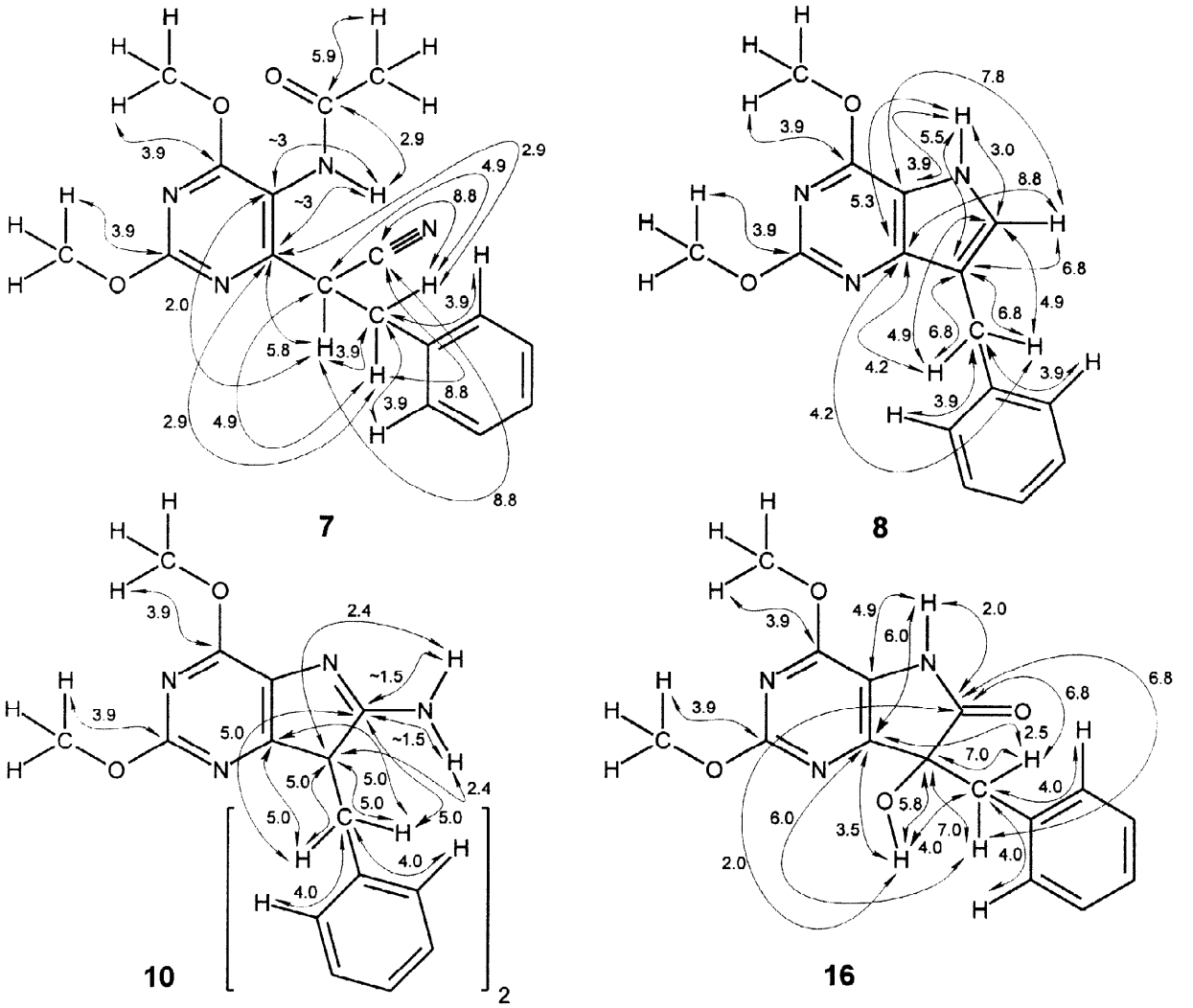


Figure 3. Long-range J(C,H) coupling constants derived from proton-coupled ^{13}C NMR spectra.

EXPERIMENTAL SECTION

General: Melting points were determined on a Kofler block and are uncorrected. Analytical TLC was performed on silica gel precoated aluminum plates with fluorescent indicator (Merck 5554, 60 F_{254}). Column chromatography was carried out on silica gel (Sigma S-0507, 40 - 63 μm). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer, using the EI (electron energy 70 eV), FAB (ionization by Xe, accelerating voltage 8 kV, thioglycerol - glycerol 3:1 mixture or 2-hydroxyethyl disulfide were used as matrixes). ^{1}H and ^{13}C NMR spectra were recorded at 500 and 127.5 MHz, respectively, on a Varian UNITY 500 instrument in hexadeuteriodimethyl sulfoxide with the solvent signal as the internal reference [$\delta(^{1}H) = 2.50$; $\delta(^{13}C) = 39.7$]. For selected compounds, in addition to the APT, proton-coupled ^{13}C NMR spectra were measured. IR spectra were obtained on a FT IR Bruker IFS 88 spectrometer in chloroform at concentration approx. 3%. UV spectra were measured on a Beckman DU-65 spectrophotometer in methanol solutions.

6-(1-Cyano-2-phenylethyl)-2,4-dimethoxy-5-nitropyrimidine (4) and
6-(2-Cyano-1,3-diphenylprop-2-yl)-2,4-dimethoxy-5-nitropyrimidine (5)

Sodium hydride (60 % wt dispersion in mineral oil, 160 mg, 4 mmol) was added to compound **3** (ref.[14]; 897 mg, 4 mmol) in 1,2-dimethoxyethane (30 mL), the red suspension was stirred at room temperature for 30 min, and a solution of benzyl bromide (595 μL, 5 mmol) in 1,2-dimethoxyethane (30 mL) was added. After stirring for 24 h, the reaction mixture was taken into ethyl acetate, washed with saturated ammonium chloride and brine, dried over magnesium sulfate, and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (24:1) gave product **4** (802 mg, 71 %) as white crystals: mp 119 - 120 °C; MS (EI): *m/z* 314 (M^+, 35), 297 (73), 284 (68), 266 (35), 258 (35), 256 (38), 242 (50), 208 (100), 91 (47); IR ($CHCl_3$): 2252 (CN), 1582 sh, 1570, 1529, 1496, 1456, 1396, 1379, 1343, 1211, 1141, 1085, 1069, 847; UV (MeOH): 271 (6.2), 257 (6.5), 213 (21.9); Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83; Found: C, 57.45; H, 4.60; N, 17.62; and product **5** (169 mg, 11 %) as white crystals: mp 131 - 132 °C; MS (EI): *m/z* 405 ($M^+ + H$, 12), 387 (53), 281 (40), 207 (37), 91 (100); IR ($CHCl_3$): 3032, 2245 (CN), 1576, 1543, 1493, 1464, 1456, 1396,1377, 1350, 1097, 1031, 991, 840; UV (MeOH): 270 (8.3), 267 (8.6), 261 (8.0), 213 (35.0); Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85; Found: C, 65.39; H, 4.95; N, 14.03.

When excess of benzyl bromide (4.8 mL, 40 mmol) was used under the above conditions, the disubstituted product **5** (1.2 g, 74 %) was obtained as the only product.

5-Amino-6-(1-cyano-2-phenylethyl)-2,4-dimethoxypyrimidine (6)

A solution of sodium dithionite (3.4 g, 40 mmol) in water (40 mL) was added to compound **4** (629 mg, 2 mmol) in methanol (40 mL), and the reaction mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was taken into ethyl acetate, washed with brine, dried over magnesium sulfate, and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (9:1) gave product **6** (330 mg, 58 %) as white crystals: mp 115 °C; MS (EI): *m/z* 284 (M^+, 100), 269 (24), 207 (15), 193 (60), 168 (23), 149 (18), 91 (56); IR ($CHCl_3$): 3440 (NH_2), 3366 (NH_2), 2244 (CN), 1587, 1484, 1468, 1405, 1380, 1261, 1191, 1089; UV (MeOH): 304 (6.0), 238 (8.1); Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71; Found: C, 63.09; H, 5.61; N, 19.56.

5-(N-Acetylamino)-6-(1-cyano-2-phenylethyl)-2,4-dimethoxypyrimidine (7)

Acetic anhydride (1 mL) was added to compound **6** (284 mg, 1 mmol) in pyridine (10 mL), and the reaction mixture was kept at room temperature overnight. The reaction was quenched by addition of excess of methanol at 0 °C. After the mixture was left at room temperature for 20 min, the solvent was evaporated, and the residue co-evaporated with toluene. Chromatography on silica gel column with toluene - ethyl acetate mixture (9:1) gave product **7** as a colorless foam: MS (FAB): *m/z* 327 ($M^+ + H$, 100); 285 (20); 91 (62); IR ($CHCl_3$): 3415 (NH), 2247 (CN), 1697, 1596, 1571, 1406, 1390, 1092; UV (MeOH): 266 (5.2), 222 (8.9); Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17; Found: C, 62.32; H, 5.51; N, 16.98.

7-Benzyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (8)

10 % Palladium on activated carbon (10 mg) was added under argon to a solution of compound **4** (314 mg, 1 mmol) in ethyl acetate - acetic acid (2:1) mixture (100 mL), and the reaction mixture was hydrogenated under slight overpressure of hydrogen overnight. The catalyst was filtered off over Celite, and the filtrate evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (24:1) gave product **8** as white crystals: mp 134 - 135 °C; MS (EI): *m/z* 269 (M^+, 100); IR ($CHCl_3$): 3474 (NH), 2953, 1630, 1564, 1546, 1488, 1467, 1384, 1370,

1299, 1235, 1079, 1041, 958; UV (MeOH): 285 sh (5.9), 268 (10.0), 225 (19.0); Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60; Found: C, 66.97; H, 5.59; N, 15.48.

5-Amino-6-(2-cyano-1,3-diphenylprop-2-yl)-2,4-dimethoxypyrimidine (9) and 6-Amino-7,7-dibenzyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (10)

A solution of sodium dithionite (3.4 g, 40 mmol) in water (40 mL) was added to compound **5** (809 mg, 2 mmol) in methanol (40 mL), and the reaction mixture was refluxed for 4 h. After removing of the solvent to a small volume, the residue was taken into ethyl acetate, washed with brine, dried over magnesium sulfate, and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (4:1) gave product **9** (268 mg, 0.7 mmol) as white crystals: mp 99 - 100 °C; MS (EI): *m/z* 374 (M^+, 36), 283 (M^+ - Bn, 100), 91 (18); IR ($CHCl_3$): 3463 (NH_2), 3382 (NH_2), 2236 (CN), 1617, 1591, 1578, 1497, 1482, 1465, 1404, 1380, 1268, 1257, 1240, 1192, 1167, 1099, 1085, 1031, 1016, 948; UV (MeOH): 305 (5.5), 237 (7.8); Anal. Calcd. for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96; Found: C, 70.36; H, 5.85; N, 14.75; and product **10** (185 mg, 0.5 mmol) as white crystals: mp 127 - 128 °C; MS (EI): *m/z* 374 (M^+, 95), 283 (M^+ - Bn, 100), 91 (33); IR ($CHCl_3$): 3511 (NH_2), 3403 (NH_2), 1627, 1584, 1552, 1496, 1473, 1465, 1457, 1384, 1367, 1077; UV (MeOH): 320 (2.7), 271 (15.0); Anal. Calcd. for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96; Found: C, 70.77; H, 5.94; N, 14.69.

For complete conversion to product **10**, a solution of compound **9** (374 mg, 1 mmol) in methanol - acetic acid 1:1 mixture (50 ml) was refluxed for 1 h. After the solvent was removed, the residue was taken into ethyl acetate, washed with saturated sodium hydrogencarbonate and brine, dried over magnesium sulfate, and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (4:1) gave product **10** (305 mg, 82 %).

6-(N-Acetylamino)-7,7-dibenzyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (11)

Acetic anhydride (1 mL) was added to compound **10** (374 mg, 1 mmol) in pyridine (10 mL), and the reaction mixture was kept at room temperature overnight. The reaction was quenched by addition of excess of methanol at 0 °C. After the mixture was left at room temperature for 20 min, the solvent was evaporated, and the residue co-evaporated with toluene. Chromatography on silica gel column with toluene - ethyl acetate mixture (4:1) gave product **11** as white crystals: mp 201 - 202 °C; MS (EI): *m/z* 416 (M^+, 44); 325 (M^+ - Bn, 72); 283 (94); 91 (100); 43 (32); IR ($CHCl_3$): 3391 (NH), 1706, 1680, 1639, 1603, 1565, 1468, 1457, 1367, 1323, 1077, 1046, 1018; UV (MeOH): 315 (6.8), 285 sh (14.6), 275 (16.7); Anal. Calcd. for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45; Found: C, 69.44; H, 5.72; N, 13.41.

6-Amino-7-benzyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (12)

10 % Palladium on activated carbon (50 mg) was added under argon to a solution of compound **5** (809 mg, 2 mmol) in methanol (500 mL) which was acidified by addition of 1 M hydrogen chloride in methanol (5 mL), and the reaction mixture was hydrogenated under slight overpressure of hydrogen overnight. Then the reaction mixture was neutralized with 1M sodium methoxide, the catalyst was filtered off over Celite, and the filtrate evaporated. Flash chromatography on silica gel column with chloroform gave product **12** (350 mg, 62 %) as a white solid contaminated with a small amount of the oxidation product **13**. Because of high sensitivity to air oxidation, compound **12** could not be isolated free of the product **13**. Nevertheless, the NMR and MS spectra were obtained: MS (FAB): *m/z* 285 (M^+ + H, 100). Compound **12** was fully characterized as the acetate **14**.

6-Amino-7-benzyl-2,4-dimethoxy-7-hydroxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (13)

Method A: Crude compound **12** (569 mg, 2 mmol) from the previous procedure was solved in chloroform (100 mL) and stirred in open flask for 4 days. After evaporation of the solvent, the residue was purified by chromatography on silica gel column with chloroform - methanol mixture (49:1) to afford product **13** (360 mg, 60 %) as white crystals: mp 248 - 249 °C; HRMS (EI): *m/z* 300.1211 (M^+, 54, Calcd.for $C_{15}H_{16}N_4O_3$: 300.1222), 209 (M^+ - Bn, 100), 91 (52); IR (KBr): 3420, 3381, 1662, 1608, 1589, 1565, 1459, 1365, 1076, 1057, 1002; UV (MeOH): 333 (3.2), 269 (19.1); Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66; Found: C, 59.78; H, 5.31; N, 18,64.

Method B: 30 % Hydrogen peroxide (1 mL) was added to a solution of crude compound **12** (284 mg, 1 mmol) in *tert*-butanol (10 mL), and the reaction mixture was left at room temperature overnight. After evaporation of the solvent, the residue was purified by chromatography on silica gel column with chloroform - methanol mixture (49:1) to give product **13** (200 mg, 67 %) as white crystals which was characterized as stated in method A.

6-(N-Acetylamino)-7-benzyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (14)

Acetic anhydride (1 mL) was added to crude compound **12** (284 mg, 1 mmol) in pyridine (10 mL), and the reaction mixture was kept at room temperature overnight. The reaction was quenched by addition of excess of methanol at 0 °C. After the mixture was left at room temperature for 20 min, the solvent was removed, and the residue was co-evaporated with toluene. Chromatography on silica gel column with chloroform gave product **14** (210 mg, 64 %) as white crystals: mp 214 - 215 °C; MS (EI): *m/z* 326 (M^+, 100), 311 (29), 283 (58), 269 (23), 207 (26), 91 (21), 43 (62); IR ($CHCl_3$): 3401 (NH), 1691, 1645, 1581, 1558, 1506, 1495, 1464, 1370, 1300, 1119, 1084, 1029; UV (MeOH): 294 (16.9); Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17; Found: C, 62.33; H, 5.55; N, 17.07.

7-Acetoxy-6-(N-acetylamino)-7-benzyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (15) and 7-Benzyl-7-hydroxy-2,4-dimethoxy-6-oxo-6,7-dihydro-5*H*-pyrrolo[3,2-*d*]pyrimidine (16)

Method A: Acetic anhydride (2 mL) was added to compound **13** (601mg, 2 mmol) in pyridine (20 mL), and the reaction mixture was stirred at room temperature for 5 days. The reaction was quenched by addition of excess of methanol at 0 °C. After the mixture was left at room temperature for 20 min, the solvent was removed, and the residue was co-evaporated with toluene. Chromatography on silica gel column with chloroform gave product **15** (425 mg, 55 %) as white crystals: mp 248 - 250 °C; MS (EI): *m/z* 384 (M^+, 40), 251 (39), 209 (100), 91 (46), 43 (59); IR ($CHCl_3$): 3368, 3338, 1752, 1654, 1602, 1582, 1480, 1381, 1369, 1328, 1244, 1078, 1046, 1018; UV (MeOH): 330 (5.5), 275 (15.6); Anal. Calcd. for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58; Found: C, 59.17; H, 5.17; N, 14.56; and product **16** (50 mg, 8 %) as white crystals: mp 245 - 247 °C; MS (EI): *m/z* 301 (M^+, 68), 91 (Bn, 100); IR ($CHCl_3$): 3301, 1743, 1714, 1665, 1624, 1472, 1408, 1358, 1198, 1149, 1088, 1068, 1006; UV (MeOH): 312 (3.0), 251 (13.0); Anal. Calcd. for $C_{19}H_{20}N_4O_5$: C, 59.80; H, 5.02; N, 13.95; Found: C, 60.05; H, 5.13; N, 13.81.

Method B: Acetic anhydride (2 mL) was added to compound **13** (300 mg, 1 mmol) in acetic acid (20 mL), and the reaction mixture was refluxed for 8 hours. The reaction was quenched by addition of excess of methanol at 0 °C. After the mixture was left at room temperature for 20 min, the solvent was removed, and the residue was co-evaporated with toluene. Chromatography on silica gel column with chloroform gave product **15** (520 mg, 68 %) which was characterized as stated in method A.

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Acknowledgment: This work was supported by the Grant Agency of the Czech Republic (Grant No. 203/96/0005, 203/96/0497, and 203/96/K0001), PECO project of the European Community (No. ERB CIPCT 940202), and by Gilead Sciences (Foster City, U.S.A.). The autors are indebted to the staff of the Laboratory of Mass Spectroscopy (Dr. K. Ubik, Head), the Laboratory of IR Spectroscopy (Dr. P. Fiedler, Head), and Analytical Laboratory (Dr. V. Pechanec, Head) of this Institute for the measurement of MS and IR spectra, and for elemental analyses. An excellent technical assistance of Ms. Yvetta Černá is gratefully acknowledged.